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MTHFR C677T polymorphism and skin color: The white man's blackness

To the Editor: The C677T polymorphism of methylenetetrahydrofolate reductase (MTHFR) gene is linked to higher homocysteine levels and risk for myocardial infarction and stroke. MTHFR catalyzes the reaction, producing methyltetrahydrofolate, the active form of folic acid, in the remethylation of homocysteine to methionine. Hyperhomocysteinemia is a known cardiovascular risk factor, with effects on gene allelic expression in uremic patients [1, 2].

The frequency of the C677T polymorphism is, in its homozygous TT form, about 20% and more in whites, and 1% or less in blacks from Africa or the United States [3]. It has been proposed that a selective advantage in possessing this variant lies in the capability to conserve folates for DNA production during times of relative folate deficiency. It is not clear why black people shouldn't possess this selective advantage.

A dark skin color has been recently envisioned as a means through which man protects himself from folate destruction because folates are highly susceptible to ultraviolet A (UVA) ray degradation. Skin color represents a delicate balance between the need to produce enough vitamin D and folate conservation, in particular when folates are scarce [4].

We put forward the hypothesis that in black people, skin color allows for some vitamin D production, while it protects from folate degradation, and no reason why the MTHFR variant should have been favored. White people instead have evolved in a population of individuals where the MTHFR TT genotype is favored for folate conservation. Little sun exposure allows for limited folate degradation, and in times of folate deficiency these individuals would produce enough folates for DNA synthesis. Therefore, the MTHFR thermolabile variant would represent "the white man's blackness."

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Mitochondrial causes of renal insufficiency and hearing loss

To the Editor: A recent paper in *Kidney International* by Izzedine et al [1] provided an excellent review of ear and kidney syndromes. We would like to call attention to another syndrome that can be associated with hearing loss and renal disease. Mutations in the mitochondrial gene *MTTL1*, which encodes tRNA $^{Leu(URR)}$, can also cause renal dysfunction and hearing loss. In the most severe form, mutations in this gene cause MELAS syndrome (Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, and Stroke), which is a multisystem disorder that can present with cerebral vascular accidents, seizures, hearing loss, cardiomyopathy, diabetes, and nephropathy. Mutation analysis of *MTTL1* in MELAS patients reveals that 80% have the mutation A3243G, 7.5% have T3271C, and 7.5% to 10% have A3253G [2].

We have evaluated three unrelated patients with the *MTTL1* A3243G mutation and features of MELAS syndrome: a 48-year-old man with a creatinine of 2.0 g/dL who presented with cardiomyopathy, diabetes, and hearing loss; a 22-year-old woman with an iothalamate clearance of 67 mL/min who presented with cardiomyopathy, history of a thalamic stroke, an elevated blood lactate, and progressive hearing loss; and a 28-year-old woman with an iothalamate clearance of 29 mL/min who presented with hypertrophic cardiomyopathy, history of a stroke,

seizures, and an elevated blood lactate with normal hearing.

The incidence of renal involvement in the MELAS syndrome is unknown, and the reported frequency of hearing loss is 75%. The *MTTL1* gene mutations should be considered in patients presenting with renal insufficiency and hearing loss.

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Gene expression analysis in microdissected renal biopsy

To the Editor: Microdissection of renal biopsy may be necessary to analyze gene expression in glomeruli and tubulointerstitium [1], but this procedure is delicate because RNA degradation may occur. The Munich group [2, 3, 4] recently reported the possibility of microdissecting biopsies stored in *RNA later*®, a commercial RNase inhibitor. We completely agree that control of RNAase activity is crucial during microdissection; nevertheless, we obtained different results that may be worthy of discussion.

The cortical tissue from five kidney biopsies taken from sites remote from tumor-bearing tissue was immediately divided under the stereomicroscope into three randomly allocated pieces: A and B were stored in *RNA later* following the protocol instructions to investigate microdissection feasibility and evaluate RNA extraction, respectively; C was kept in saline containing 100 U of *RNAsin*® at 4°C. After 1 hour of storing in *RNA later*, pieces A were microdissected; but although our experience includes over 150 renal biopsies, we had trouble separating glomeruli from the tubulointerstitium. Indeed, fragments of a homogeneous yellowish color appeared at the stereomicroscope, glomeruli could be hardly recognized, and specimens appeared compact and stiff, resembling fixed tissues. On the contrary, from pieces C it was possible to collect easily 10 to 20 glomeruli each.

We agree with the authors in reference to the quality (yield and purity) of extracted RNA from the cortical tissue of pieces B. Thus, in our experience storing tissues in *RNA later* represents an optimal mean to preserve RNA from degradation, but does not warrant microdissection of the biopsy.

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Can error in GFR formulas explain their poor performance in transplant patients?

To the Editor: In a recent paper by Mariat et al [1], the performance of several glomerular filtration rate (GFR) equations was assessed against inulin clearance in renal transplant patients. One of the GFR estimate equations used was the Nankivell formula, which was printed as the following:

GFR (mL/minute) = 6.7/serum creatinine + 0.25 × weight – 0.5 × urea – 0.01 × height^2 + 35(25 for woman).

However, on review of Dr. Nankivell's original article [2], the original formula derived was:

GFR (mL/minute) = 6.7/creatinine (mmol/L) + BW(kg)/4 – urea(mmol/L)/2 – 100/height(m)^2 + 35 (25 for woman).

If this was not a printing error and this formula was applied to the data, this may account for the relative decreased accuracy of the Nankivell formula when compared with the other GFR calculation equations.

In addition, the Levey formula (Mariat et al [1]) was printed as:

GFR (mL/minute) = 170 × serum creatinine$^{-0.999}$ × age$^{-0.1}$ × 0.762 (if woman) × 1.180 (if patient is black)